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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LAM, ANN Y	

ART UNIT	PAPER NUMBER
1641	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/645,874	BUECHLER ET AL.	
	Examiner	Art Unit	
	ANN Y. LAM	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 50 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 and 6 of copending Application No. 12/391,157. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Claim 50 of the present application essentially encompasses claim 1 of Application 12/391,157, except that claim 1 of the Application 12/391,157 recites administering the dipeptidyl peptidase inhibitor whereas the present invention recites "determining a treatment regimen" that "includes one or more inhibitors of prolyl-specific DPP". However administering is a well known and common means of treatment with a therapeutic compound and is also a general term that encompasses a wide variety of means to treat with a therapeutic compound, and thus would have been an obvious means for carrying out a treatment regimen. Also, while Claim 50 of the present application does not recite "for treatment of cardiovascular disease or heart failure", it does recite "a treatment regimen" and "selecting said subject on the basis of a diagnosis of congestive heart failure, acute coronary syndrome or acute myocardial infarction", and thus it is understood that the treatment is for these conditions.

Claim 50 of the present application also recites acute myocardial infarction, which is recited in claim 6 of Application 12/391,157.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

(It is noted that independent claims 18, 21 and 25 of Application 12/391,157 recite the same or similar steps as claim 50 of the present Application, but that they additionally recite "in an amount sufficient to inhibit degradation of B-type natriuretic peptide in said subject". Since claim 29 of the present Application, which also recited such limitations, has been canceled, a provisional obviousness-type double patenting rejection over these claims is not being made.)

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 50-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test to determine whether a claimed invention is enabled is whether a person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 8 USPQ2d 1400, 104 (Fed. Cir. 1988). Whether there would be undue experimentation is determined by analyzing the factors set out in the *Wands* case.

Known as the Wands factors, they include (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) existence of working examples and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time of the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

I. Wand Factors

The Wands factors are described in depth below.

i. Breath of the claims

The claims are broad, directed to determining a treatment regimen based in part on the presence or amount of the natriuretic peptide BNP (77-108) wherein the regimen includes one or more inhibitors of prolyl-specific DPP. The inhibitor is not limited to any particular type of compound, nor is the manner of administration specified. (Dependent claims 51 and 52 recite further specifics regarding the DPP inhibitor, but still recite broad categories of compounds rather than a particular type of compound, and a manner of administration is also not specified.)

ii. Nature of the invention

The invention is directed to a method of determining a treatment regimen for a subject wherein the regimen includes one or more inhibitors of prolyl-specific DPP.

Applicant discloses that the DPP inhibitor prevents DPP from cleaving proline in the penultimate position of mature BNP [BNP (77-108)], thereby preventing its degradation. See Specification, paragraph 0046. It is also disclosed that the inhibition improves the potential for BNP to act as a therapeutic agent. Paragraph 0046. BNP (77-108) is also involved in regulating blood pressure and fluid balance. Paragraph 0005.

iii. State of the prior art

The prior art describes using various sections of the full-length BNP molecule as a marker for various diseases, including congestive heart failure. See Cheng et al. J. Am. Coll. Cardio. (2001) 37:386-391 ("Cheng") (using the mature portion, i.e., BNP (77-108)); U.S. 5,786,163 ("Hall") (using BNP (1-76)); and U.S. 6,124,430 ("Mischak") (using portions between amino acids in the 1 and 25 position.) The prior art also describes that a DPP inhibitor can be administered to a patient to treat congestive heart failure. See U.S. Patent Appl. Pub. No. 2004/0167341 ("Haffner".) However Haffner does not appear to provide sufficient guidance on using a DPP inhibitor for inhibiting the degradation of BNP molecules in a subject selected based on congestive heart failure (or acute coronary syndrome or acute myocardial infarction.) Applicants also made this argument in traversing the combination of Cheng and Haffner used to reject claims 29-33 and 43-49. See Response filed August 7, 2009. Instead, Haffner appears to generally teach inhibiting DPP to treat a variety of diseases with no specific guidance on how DPP operates. Accordingly, Haffner describes various portions of BNP useful as markers for congestive heart failure, but does not teach administering a DPP inhibitor to inhibit degradation of, e.g., BNP (77-108).

Furthermore, U.S. Patent App. Pub. No. 20020061839 ("Scharpe") (newly cited) discloses compounds (e.g. of claim 1) that are found to be very potent modulators, in particular inhibitors, of serine peptidases/proteases in general, and DPP IV (dipeptidyl peptidase IV), DPP II (dipeptidyl peptidase II), in particular. The compounds as listed in claim 12 were found to be potent inhibitors of DPP IV. Paragraph 0014. Scharpe further discloses that the compounds of the invention can be used for prevention and treatment of thrombosis and conjunction therapy of acute myocardial infarction by specifically inhibiting Factor X, thrombin and Factor VII (factor VII-Tissue Factor). Paragraph 0112. However, Scharpe does not disclose any correlation that suggests determining a treatment regimen, including inhibitors of DPP, based in part on the presence or amount of any BNP. [It is noted that the assay to detect natriuretic peptide (BNP 77-108) is a step for determining a treatment regimen based in part on the presence or amount of the natriuretic peptide, as implied in independent claim 50, rather than merely a step performed for the diagnosis of congestive heart failure, acute coronary syndrome or acute myocardial infarction (a diagnosis of which is required in the selecting of the subject for treatment, as recited in independent claim 50.)] Scharpe does not disclose a specific correlation between BNP and DPP inhibitors, nor as Applicant has found, that DPP inhibitors prevent degradation of BNP and thus can be administered for treating a subject in need of *increase* natriuretic peptide function. Accordingly, Scharpe does not teach a treatment regimen including a DPP inhibitor based on the presence or amount of the natriuretic peptide detected.

iv. Level of one of ordinary skill in the art

The level of ordinary skill in the art is high.

v. Level of predictability in the art

The level of predictability in the art is extremely low. As noted above, the prior art provides ample description of using different portions of BNP as a marker for congestive heart failure, including BNP (77-108), but does not provide sufficient guidance for administering a DPP inhibitor, in general, in a subject with congestive heart failure, acute coronary syndrome or acute myocardial infarction, nor for administering a DPP inhibitor specifically to inhibit degradation of the BNP. Haffner, as the only reference that describes using DPP inhibitor to treat congestive heart failure, merely cites the disease in a prophetic example under a long list of diseases that Haffner alleges can be treated with the inhibitor. Applicants strongly argue this point in their previous responses, highlighting the unpredictability of the prior art in establishing that a DPP inhibitor can prevent the degradation of any BNP peptide, much less BNP (77-108).

Likewise, Scharpe, as the only reference that describes using DPP inhibitor to treat acute myocardial infarction, does not provide sufficient guidance for administering a DPP inhibitor to inhibit degradation of BNP. Nor does Scharpe disclose any correlation that suggests determining a treatment regimen, including inhibitors of DPP, based in part on the presence or amount of any BNP, as recited in the claims. That is, Scharpe does not disclose a specific correlation between BNP and DPP inhibitors, nor as Applicant has found, that DPP inhibitors prevent degradation of BNP and thus can be administered for treating a subject in need of *increase* natriuretic peptide function.

Applicants have also emphasized the unpredictability of the prior art in establishing that a DPP inhibitor can prevent the degradation of any BNP peptide, much less BNP (77-108).

vi. Amount of direction provided by the inventor

Applicants have provided little direction to allow one of ordinary skill in the art to successfully practice the claimed invention. Indeed, Applicants only provide a general description on how DPP inhibitors operate *in vivo* with no concrete direction or steps on how to effectuate such inhibition. For example, paragraphs 0127 and 0129 generally describe steps for selecting and screening for DPP inhibitors, but do not relate these steps for selecting specific DPP inhibitors that would work on inhibiting BNP degradation *in vivo*. Instead, Applicants refer to prior art describing specific DPP inhibitors for managing diabetes. See paragraph 0126. However, diabetes does not appear to have any relationship to congestive heart failure, acute coronary syndrome or acute myocardial infarction with respect to DPP inhibition. The general preparatory methods are therefore too broad to provide the skilled artisan with insight on how to select DPP inhibitors specific for the claimed invention.

vii. Existence of working examples

Applicants have not provided any working examples germane to showing that a DPP inhibitor can actually prevent degradation of BNP (77-108) *in vivo*. Indeed, the only relevant working examples provided describe the assaying of BNP without reference to obtaining a sample from a subject (Example 3), synthesis of DPP inhibitors without describing their use *in vivo* (Example 4), and the purification and assay of DPP

peptides. None of these examples actually describe a process of selecting an appropriate DPP inhibitor for inhibiting degradation of BNP (77-108), administering the inhibitor to a subject, and then assaying a biological sample from the subject to determine whether BNP inhibition has taken place.

It is noted that while claim 50 (and its dependent claims) do not recite that the treatment regimen including one or more inhibitors of proly-specific DPP is ---to inhibit degradation of natriuretic peptide by prolyl-specific DPP--, the claim is nevertheless directed to a method of "determining a treatment regimen *based in part on the presence or amount of said natriuretic peptide*" (as recited in claim 50, emphasis added.) However there are no working examples showing a treatment regimen based in part on the presence or amount of a natriuretic peptide. The claims as well as the specification appear to lack a disclosure on the relationship between the detection of the natriuretic peptide and the treatment regimen that is supposed to be based in part on the presence or amount of the natriuretic peptide. Due to this lack of disclosure and due to a lack of a working example, it is not clear as to whether the mere presence of the recited natriuretic peptide or a certain amount of the natriuretic peptide (and if so, what amount) would be sufficient as a basis for determining a treatment regimen; and it is also not clear as to what that treatment regimen would be (e.g. amount of prolyl-specific DPP and manner of treatment) based on the detected natriuretic peptide.

It is also noted that the mere term "treatment regimen" (as recited in independent claim 50) implies that the regimen *treats* a condition, but there is no working example showing a regimen that treats a condition, much less a regimen that

is based in part on the presence or amount of natriuretic peptide, that treats an underlying condition (for example, by inhibiting degradation of a natriuretic peptide *in vivo.)* It is noted that there is no working example to show what type of proly-specific DPP or how much of it or what manner of treatment would be effective in a treatment.

viii. Quantity of experimentation needed

The quantity of experimentation needed is great. As noted above, the prior art does not provide guidance on which DPP inhibitors are appropriate to inhibit degradation of BNP molecules or would work as a treatment regimen based on detected BNP. Moreover, Applicants' specification lacks any guidance or working example for doing the same or indicating that such inhibition actually occurs. Accordingly, one of ordinary skill in the art would not be able to perform the claimed invention without performing undue experimentation.

II. Analysis of the Wands Factors

With the foregoing analysis in mind, one of ordinary skill in the art would not be able to perform the claimed invention without undue experimentation. The claims are broad--directed to a method of using any prolyl-specific DPP inhibitor as part of a treatment regimen based in part on the detected presence or amount of the mature natriuretic peptide BNP (77-108); however, neither the prior art nor Applicants' specification provides sufficient guidance for accomplishing this method. Applicants acknowledge that the prior art is lacking in sufficient description. However, Applicants themselves have not provided sufficient information in the form of working examples or other guidance to allow the skilled artisan to practice the invention without performing

undue experimentation. Accordingly, the instant claims are rejected as lacking enablement.

Response to Arguments

It is acknowledged that Applicants have amended the claims to avoid the rejections made in the previous Office action [which were made by a different examiner]. However, upon further consideration, it is found that claim 50 should have been rejected for lacking enablement, as described above. It is noted that the above rejections are based on almost the same analysis as set forth in the last Office action regarding independent claim 29 (now canceled), but with further elaboration with respect to claim 50. Also a new reference (U.S. patent to Scharpe) is cited.

Moreover, a new provisional obviousness double patenting rejection is made above.

It is noted that the present Office action is made non-final.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: U.S. Patent App. Pub. Nos. 20070293474, 20080045444, 20090275512.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANN Y. LAM whose telephone number is (571)272-0822. The examiner can normally be reached on Mon.-Thurs. 9-7:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ann Y. Lam/
Primary Examiner, Art Unit 1641